Aromatase inhibitors in the treatment of endometriosis

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Abstract

Endometriosis is a chronic inflammatory condition in which foci of endometrial tissue grow outside of the uterine cavity. Endometriosis was estimated to affect 176 million women of childbearing potential all over the world in 2010. The presence of extrauterine endometrial tissue is associated with pain and infertility. Typical symptoms of endometriosis include dysmenorrhoea, dyspareunia, heavy menstrual periods (menorrhagia), pelvic pain that is not related to menstrual cycles, dysuria, and chronic fatigue. Medical treatments for endometriosis include combined oral contraceptive pills, danazol, gestrinone, medroxyprogesterone acetate, and gonadotropin-releasing hormone agonists (aGnRHs). A new class of medications called aromatase inhibitors has been identified in recent years as potential therapeutic agents for endometriosis. This article provides general information about aromatase inhibitors, their use in gynaecology, and their adverse effects. In particular, the paper discusses the use of aromatase inhibitors in the treatment of endometriosis in postmenopausal women. Unlike oral contraceptives, gestagens, aGnRHs, and danazol, which suppress ovarian oestrogen synthesis, aromatase inhibitors inhibit mainly extra-ovarian synthesis of oestrogens. Therefore, the use of aromatase inhibitors seems to be particularly relevant in older patients, as most of the body's oestrogen is produced outside the ovaries after menopause. The paper discusses also the use of aromatase inhibitors in the treatment of pain associated with endometriosis and infertility caused by endometriosis.

Key words: aromatase inhibitors, endometriosis.

Introduction

Endometriosis is a chronic inflammatory condition in which foci of endometrial tissue grow outside of the uterine cavity. The presence of extrauterine endometrial tissue is associated with pain and infertility. Endometriosis was estimated to affect 176 million women of childbearing potential all over the world in 2010 [1]. It is hypothesised that ectopic endometrial tissue is transplanted by retrograde menstruation (a reversal in the direction of menstrual flow), arises by endometrial metaplasia of the peritoneal serosa, or is carried through the lymphatic system to distant organs in women with a genetic or immunologic predisposition to the disease [1]. Some authors also suggest possible involvement of neurological factors in the aetiopathology of endometriosis [2] and point to the relationship between signs and symptoms of endometriosis and the level of oestrogens [3].

Typical symptoms of endometriosis include dysmenorrhoea, dyspareunia, heavy menstrual periods (menorrhagia), pelvic pain that is not related to menstrual cycles, dysuria, and chronic fatigue [4]. Endometriosis may cause infertility due to tubal blockage, ovarian cysts, subclinical pelvic inflammatory disease, poor oocyte quality, and impaired endometrial receptivity [5]. In addition, endometriosis may worsen clinical outcomes in patients treated with assisted reproductive technology (ART) [6]. Endometriosis is a significant social and economic problem [4, 7, 8].

Medical treatments for endometriosis include combined oral contraceptive pills, danazol, gestrinone, medroxyprogesterone acetate, and gonadotropin-releasing hormone agonists (aGnRHs). A new class of medications called aromatase inhibitors has been identified in recent years as potential therapeutic agents for endometriosis.

Aromatase inhibitors: background information

Aromatase is an enzyme that belongs to the cytochrome P450 superfamily. Aromatase enzyme is expressed in ovarian granulosa cells, placental syncytiotrophoblast, adipose tissue, brain, and skin fibroblasts. The primary sources of aromatase are ovarian granulosa cells in premenopausal women and adipose cells in postmenopausal women. Aromatase inhibitors suppress oestrogen synthesis in the ovaries and in pe-

ripheral tissues, starting from the next day after dosing. They work by inhibiting the action of aromatase, which converts androgens into oestrogens (testosterone into estradiol and androstenedione into oestrone) [9].

There are three generations of aromatase inhibitors (AIs). Aminoglutethimide is a first-generation aromatase inhibitor. The second-generation inhibitors include fadrozole and formestane. Anastrozole, letrozole, and exemestane are third-generation inhibitors. Aminoglutethimide is administered by intramuscular injection to induce medical adrenalectomy. The common side effects of treatment with aminoglutethimide include somnolence, skin rash, and nausea. The second-generation aromatase inhibitors are associated with less severe side effects, and they are also administered as intramuscular injections. The most potent, selective, and reversible inhibitors are the third-generation AIs. In general, they are administered by oral route. The third-generation AIs decrease serum 17β-estradiol by 97-99% as early as 24 hours after dosing. They also increase FSH levels in premenopausal women. Side effects of the third-generation AIs include vaginal dryness, hot flushes, headache, back pain, numbness in lower extremities, and arthralgia, which are primarily associated with low oestrogen levels [10].

Aromatase inhibitors were first used in the treatment of breast cancer. Currently, they represent 'standard of care' adjuvant therapy for oestrogen receptor-positive (ER+) breast cancer in postmenopausal women. The standard treatment for postmenopausal women consists of aromatase inhibitor for five years or tamoxifen followed by aromatase inhibitor for a total of five years. Clinical trials demonstrated that, unlike other treatments, aromatase inhibitors did not increase the risk of ischaemic heart disease in this population of patients [11].

Aromatase inhibitors in the treatment of pain associated with endometriosis

The use of AIs in the treatment of endometriosis was based on the evidence of aromatase activity in ectopic endometrial lesions, and the relationship between the presence of extrauterine endometrial tissue and serum oestrogen levels. Aromatase activity is absent in normal human endometrium and is increased in endometriosis [9]. It was demonstrated that extrauterine endometrial tissue is a source of oestrogens. Moreover, oestrogens stimulate synthesis of PGE2, which is a potent inducer of aromatase activity in endometrium. This is the underlying mechanism that triggers the virtuous cycle leading to the new growth of ectopic endometrial tissue [10]. The use of aromatase inhibitors in the treatment of endometriosis is supposed to stop this virtuous cycle.

The clinical efficacy of aromatase inhibitors for the treatment of endometriosis has been confirmed in nu-

merous clinical trials. Nawathe *et al.* [11] performed a meta-analysis of eight clinical studies that enrolled a total of 137 women. The authors demonstrated that aromatase inhibitors decreased pain, reduced the size of extrauterine endometrial lesions, and improved patients' quality of life when used in combination with gestagens, oral contraceptives, or gonadotropin-releasing hormone agonists (aGnRHs). One of the studies in this meta-analysis was a randomised controlled study. It showed that the use of aromatase inhibitors for six months in combination with aGnRH (1.0 mg anastrozole + 3.6 mg goserelin) was associated with a significant decrease in pain compared to aGnRH alone (3.6 mg goserelin) ($p < 0.0001$), and significant improvement in patient-reported symptom severity (Multidimensional Patient Scores [$p < 0.0001$]). No significant loss of bone mineral density (BMD) was detected at the spine or femoral neck.

Ferrero *et al.* [12] performed a meta-analysis of 10 clinical studies that enrolled a total of 251 women. They demonstrated that aromatase inhibitors decreased pain and improved quality of life when used in combination with gestagens or oral contraceptives in patients with endometriosis. One of these studies showed that combination treatment with letrozole and norethisterone acetate was more effective than norethisterone acetate alone in reducing pain and dyspareunia. Moreover, letrozole in combination with norethisterone acetate was associated with less severe side effects and fewer discontinuations than concomitant treatment with letrozole and a GnRH agonist, triptorelin [13]. Letrozole administered in combination with aGnRH for six months after surgery was superior to aGnRH monotherapy in patients with endometriosis [14, 15]. The ESHRE (European Society of Human Reproduction and Embryology) guidelines recommend concomitant use of aromatase inhibitors and oral contraceptives, progestogens, or aGnRHs in patients with pain associated with drug-resistant and surgery-resistant recto-vaginal endometriosis [16, 17].

Aromatase inhibitors in the treatment of postmenopausal endometriosis

Aromatase inhibitors are being considered as potential treatments for postmenopausal endometriosis. The estimated incidence rate of endometriosis is 2-5% in postmenopausal women. Surgery is preferred over non-surgical treatment in this population of patients due to the risk of cancer development. However, surgery is associated with recurrence of endometriosis, and not all older patients are eligible for this treatment. Unlike oral contraceptives, gestagens, aGnRHs, and danazol, which suppress ovarian oestrogen synthesis, AIs inhibit mainly extra-ovarian synthesis of oestrogens. Therefore, the use of aromatase inhibitors seems to be

particularly relevant in older patients, as most of the body's oestrogen is produced outside the ovaries after menopause. Polyzos et al. [18] demonstrated that treatment with letrozole and anastrozole for 4-15 months reduced pain in all patients with endometriosis. In addition, letrozole decreased urinary and gastrointestinal tract symptoms associated with endometriosis. Symptomatic improvement was achieved with letrozole in one patient who did not respond to previous treatment with exemestane (administered for 15 days). Aromatase inhibitors significantly reduced the size of ectopic endometrial lesions as measured by imaging studies [19]. Only one patient with ureteral endometriosis did not respond to treatment with anastrozole (for 15 months) due to significant ureteral fibrosis requiring surgical intervention [20]. Hot flushes were observed in one patient at four months of treatment with letrozole, and completely resolved without recurrence of pain after administration of micronised oestradiol at a dose of 0.5 mg/day. A Decrease in bone mineral density (BMD) was reported in one patient after nine months of treatment with anastrozole.

Aromatase inhibitors in the treatment of infertility caused by endometriosis

Another important issue we should address is treatment of infertility in patients with endometriosis. Many reports suggest lower effectiveness of drug treatment in patients with infertility caused by endometriosis [16, 17, 21, 22]. Randomised clinical trials provide some evidence that intrauterine insemination (IUI) with ovulation induction may be effective in patients with mild to moderate endometriosis [16, 17, 23, 24]. Werbrouck et al. [25] demonstrated that ovulation induction treatment and IUI within six months of surgery may have positive outcomes in patients with mild to moderate endometriosis. Aromatase inhibitors were first used in ovulation induction treatment in 2001 [26]. Their mechanism of action involves stimulation of pituitary secretion of FSH through the prevention of oestrogen formation from androgens. It was also found that increased interfollicular androgen levels enhance follicular responsiveness to FSH [27, 28]. For ovulation induction letrozole is administered at a dose of 2.5-7.5 mg/day on days 3-7 of the menstrual cycle [29]. When compared to clomiphene, letrozole inhibits oestradiol synthesis rather than its oestrogenic activity. In addition, the half-life of letrozole (~2 days) is much shorter then that of clomiphene (~2 weeks). Therefore, the drug has no anti-oestrogenic effect on cervical mucus or endometrium. Letrozole, like clomiphene, is indicated in women with polycystic ovary syndrome (PCOS) and idiopathic infertility [29-31].

Alborzi et al. [15] compared pregnancy rates and the recurrence rate of endometriosis in 144 women who were treated for two months after laparoscopic surgery for endometriosis. Patients were allocated to one of the following treatment groups: Group 1: 47 subjects treated with letrozole 2.5 mg/day; Group 2: 40 subjects treated with triptorelin 3.75 mg IM injections every 4 weeks; Group 3: 57 subjects who received no active treatments. There was no difference between treatment groups in pregnancy rates (23.4% in Group 1 vs. 27.5% and 28.1% in Group 2 and Group 3, respectively) or recurrence rate of endometriosis (6.4% in Group 1 vs. 5% and 5.3% in Group 2 and Group 3, respectively).

Abu Hashim et al. [32] compared ovulation and pregnancy rates after ovulation induction with letrozole or clomiphene and intrauterine insemination in 136 women with primary infertility, who did not conceive within 6-12 months of laparoscopic surgery for mild to moderate endometriosis. Patients were treated with letrozole 5 mg/day (69 patients, 220 cycles) or clomiphene 100 mg/day (67 patients, 213 cycles) for five days and intrauterine insemination for four cycles. Success rates for pregnancy per cycle and total number of pregnancies were comparable in both treatment groups (15.9% vs. 14.5% and 64.7% vs. 57.2% in the letrozole and clomiphene groups, respectively), even though the number of follicles and serum estradiol levels were significantly higher in the clomiphene group on the day hCG was administered. There were two twin pregnancies in the clomiphene group. Miscarriage and live birth rates were 11.4% vs. 12.9% and 44.9 vs. 40.3 in the letrozole and clomiphene groups, respectively. The authors concluded that letrozole was not superior to clomiphene ovulation induction in combination with a timed intrauterine insemination in patients with mild to moderate endometriosis, who did not conceive within 6-12 months of laparoscopic surgery.

The effect of letrozole on IVF outcomes was also investigated. Lossl et al. studied the impact of anastrozole and aGnRH on IVF outcomes in 20 infertile women with ovarian endometrioma, who underwent IVF/intracytoplasmic sperm injection [33]. Patients received goserelin 3.6 mg SC injection on day 1, day 28, and day 56 in combination with anastrozole 1.0 mg daily on 1-69 days of the treatment period. Then, ovulation induction was started on Day 70. The authors found that treatment with anastrazole and goserelin significantly reduced the size of ovarian lesions and serum CA-125 levels. The mean decrease in endometrioma volume was 29% ($p = 0.007$), and the mean decrease in serum CA-125 levels was 61% ($p = 0.001$) on days 1-70 of the treatment period. The average number of oocytes retrieved during IVF/intracytoplasmic sperm injection treatment cycles was 7.5 (range: 6.0-10.0). The rate of pregnancy was 45% (9 of 20 subjects). Four patients had a biochemical pregnancy, two had an early miscarriage, and only three (15%) patients gave birth to full-term babies. Although such a high rate of miscarriage (6 of 20

patients) could be accidental, the authors suggest the potential contribution of poor oocyte/endometrium quality due to long-term administration of oestrogen-blocking drugs.

Side effects of aromatase inhibitors

Long-term use of aromatase inhibitors is associated with increased risk of osteoporosis and bone fractures [18, 30]. The incidence of fractures was 2-11% in women receiving aromatase inhibitors as adjuvant therapy for breast cancer [34, 35]. The incidence of bone fractures was 11% ($n = 3092$) in the anastrozole group and 7.7% ($n = 3094$) in the tamoxifen group after five years of treatment. The incidence of bone fractures was 9.3% among patients receiving letrozole and 6.5% in those treated with tamoxifen after five years of treatment. After six months of treatment with exemestane, BMD decreased by 2.6% ($n = 78$) at the lumbar spine. The ASCO (American Society of Clinical Oncologists) guidelines recommend BMD testing once a year to all patients receiving aromatase inhibitors as adjuvant therapy for breast cancer, and treatment with bisphosphonates for those with BMD T-scores ≤ -2.5 [36]. After six months, combination treatment with anastrozole and goserelin was associated with a greater decrease in BMD than was goserelin alone. This effect was maintained after discontinuation of treatment. However, no patient developed osteoporosis or osteopaenia [14].

Disclosure

Authors report no conflict of interest.

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